

RESPONSE

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REMARKS

In paragraph 3, on page 2 of the Office Action, the Examiner newly rejects Claims 9-10 as being unpatentable over Slavin et al in view of Ildstad and Zhang et al and newly cited Sachs.

Specifically, as noted on page 3 of the Office Action, it is the Examiner's position that Slavin et al teaches a method involving total body radiation (TBI) and that when TBI is used, it should be used at a dose level that causes no severe or irreversible pancytopenia. Further, the Examiner contends that Slavin et al teaches transplantation of an organ into the recipient within the same day as whole bone marrow cells are administered, and achieving an engraftment rate of 100%.

The Examiner also contends that Ildstad teaches the advantages of using TBI, at column 9, lines 15-20 thereof, where it is taught that "the importance of the hematopoietic niches or "space" contributed by the low dose of TBI is even more evident when TBI is given one week prior to bone marrow transplantation.

On page 4 of the Office Action, the Examiner contends that Zhang et al teaches the equivalency between intravenous and portal vein injections of bone marrow cells.

Finally, at the bottom of page 4 of the Office Action, the Examiner newly cites Sachs for teaching a method of inducing immunological tolerance in an organ transplantation recipient by subjecting the recipient to TBI prior to administering the recipient tolerogen effective amount of bone marrow cells, and that TBI can be performed one day prior to administration of

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bone marrow cells to eliminate the recipient's endogenous BMC to stimulate hematopoiesis of the newly introduced foreign BMC.

On page 5 of the Office Action, the Examiner maintains that one have been motivated to combine sublethal TBI, about 7.0 Gy as taught by Ildstad and performing irradiation one day prior to administration of BMC as taught by Sachs and administration of bone marrow cells via the hepatic portal vein as taught by Zhang et al in a method of inducing immunotolerance in an organ transplantation recipient as taught by Slavin et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The subject matter of Claim 9 can be broken down into five steps (a) to (e), as follows:

- (a) prior to organ transplantation from a graft donor, subjecting the recipient to **total body irradiation (TBI)**, using a sublethal radiation dose of at least 6.5 Gy, and thereafter,
- (b) administering to the recipient a tolergen effective amount of **whole bone marrow cells (WBMC)** from said graft donor by hepatic portal venous administration (**p.v. administration**), and thereafter,
- (c) transplanting an organ from said graft donor into said recipient, to thereby **achieve an engraftment rate of 100%**,
- (d) wherein said subjecting the recipient in step (a) is performed **one day prior** to said administering of WBMC in step (b); and

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(e) wherein said transplanting an organ in step (c) occurs **within the same day** as said administering of WMBC in step (b) (**one-day protocol**).

The table below summarizes the teachings of each of the cited references with respect to the limitations of Claim 9.

Claim 9	Slavin et al		Ildstad et al	Zhang et al	Sachs
	(1) TLI	(2) TBI			
(a) TBI	No	Yes (4Gy)	Yes (7Gy)	No	Yes (4Gy)
(b) p.v. of WMBCs	No (i.v.)	No (i.v.)	No (i.v.)	Yes (p.v.)	No (i.v.)
(c) Engraftment rate of 100%	Yes	No	No (not donor's skin)	No	No
(d) One day between (a) and (b)	No	No	No (1 week)	No	Yes (1 day)
(e) One-day protocol	Yes	No	No (1-7 months)	No	No

The Examiner appears to contend that Slavin et al teaches limitations (a), (c) and (e) of Claim 9. Further, the Examiner appears to contend that limitations (a) (7Gy), (b) and (d) of Claim 9, which are not taught in Slavin et al, would be easily predicted from the disclosures of the secondary references.

However, Applicants respectfully submit that the Examiner's assertion is being made without a clear understanding of the teachings of Slavin et al, and can only be made in hindsight, which is legally improper.

As shown in the table above, clearly Slavin et al teaches as separate techniques:

(1) a technique using TLI (see, for example, the claims thereof and Example 14 of Slavin et al, wherein (c) and (e) are taught), and

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(2) a technique using TBI (see column 8, lines 57-67 and Examples 10 and 11, wherein (a) is taught).

Slavin et al does not teach that the two techniques may be used interchangeably, much less equivalently. Such equivalency was not known in the art prior to the effective filing date of the present application.

If only (1), the technique using TLI of Slavin et al is focused on, it is clear that this technique is fundamentally different from (2), the technique using TBI. Therefore, a skilled artisan would never expect a combination of the TLI technique of Slavin et al with those of the secondary references.

If only (2), the technique using TBI of Slavin et al, is focused on, it may be possible for a person skilled in the art to combine this technique with that disclosed in Ildstad et al and Sachs. However, from any combination of these references, a skilled artisan could not have arrived at the present invention, since none of these references disclosed both limitations (c) and (e) of the present invention.

As discussed above, there is no technical basis for the Examiner's assertion that a person skilled in the art would have arrived at the present invention from the teachings of the cited references.

More specifically, Slavin et al discloses (1), a technique using TLI and (2) a technique using TBI, wherein only (1) the technique using TLI (Example 14), employs limitations (c) and (e). Slavin et al does not teach or suggest that (c) and (e) can be achieved using (2), i.e., the technique using

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TBI. Rather, Slavin et al teaches that (c) and (e) can not be achieving TBI (see Figures 4 and 7).

As noted by Applicants, in the Response After Final filed February 20, 2004, the descriptions of Slavin et al cited by the Examiner (column 13, lines 50-67 and column 14, lines 10-15) do not relate to results obtained by employing TBI. TBI was not conducted in Example 14 of Slavin et al, but rather total lymphoid irradiation (TLI) was used, which is fundamentally different from TBI (see the description "non-myeloablative conditioning (e.g., TLI) (day 0)", in column 14, lines 13-14 of Slavin et al. In contrast, TBI is "myeloablative conditioning"). As discussed in the Response dated July 28, 2003, TLI is fundamentally different from TBI.

Furthermore, (2) the technique using TBI taught by Slavin et al is fundamentally different from that of the present invention in the following ways:

- (i) TBI is conducted at an irradiation dose of 4.0 Gy in Slavin et al (see Examples 10 and 11, which is much less than that claimed in the present invention (at least 6.5 Gy).
- (ii) The BMC administration route is intravenous (i.v.) (see Column 29, line 2 and Column 36, line 15), not portal vein (p.v.), as claimed in the present invention.
- (iii) Slavin et al does not disclose that an engraftment rate of 100% is achieved, as claimed in the present invention.

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(iv) Slavin et al does not disclose that step (a) is preformed one day prior to the step (b), as claimed in the present invention.

(v) Slavin et al does not disclose transplanting an organ into a recipient who has undergone TBI within the same day as the WMBC administration, as claimed in the present invention.

Looking at only the teachings of Slavin et al, it is clear that a skilled artisan would never arrive at achieving (c) and (e) by using TBI, instead of TLI. Moreover, none of the cited references teach that (c) and (e) can be achieved (see the above table), other than wherein using the TLI technique of Slavin et al.

Accordingly, Applicants respectfully submit that Slavin et al does not teach or suggest the present invention, and for the following reasons, it is clear that the combination thereof with Ildstad et al and Zhang et al and Sachs can only be made in hindsight, which is legally improper.

Ildstad et al teaches TBI at 7Gy. However, there is no motivation in Ildstad et al or Slavin et al to conduct TBI at 7 Gy in (1) the technique using TLI of Slavin et al (the only technique discussed in Slavin et al that can achieve (c) and (e)).

Furthermore, with regard to (2), the technique using TBI of Slavin et al, while a skilled artisan might have used 7Gy-TBI instead of 4Gy-TBI in view of the teachings of Ildstad et al, a person skilled in the art could not have predicted whether (c) and (e) could be achieved by such a combination.

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Zhang et al merely discloses the results of a comparison between i.v. and p.v. in a system without irradiation. Applicants respectfully submit that it is impossible to predict whether similar effects occur in a system with irradiation, as is claimed in the present invention.

Thus, the Examiner's combination of the teachings in Zhang et al with Ildstad and Slavin et al can only be made in hindsight which is legally improper.

Moreover, Zhang et al nowhere teaches that (c) and (e) can be achieved by p.v. administration, as claimed in the present invention.

The technique (2) taught by Slavin et al, wherein immunological tolerance is achieved by employing TBI and the technique disclosed in Zhang et al, wherein irradiation is not preformed, are fundamentally different in terms of whether or not the recipient's general immune system itself is damaged. One skilled in the art would not have expected that the difference in results attributable to the different administration routes, i.e., i.v. vs. p.v., in Zhang et al would be applicable to a recipient who has undergone TBI. This is because the immune system and the liver of the recipient are damaged by TBI, whereas in the technique of Zhang et al, such are not damaged, and hence, rejection of administered BMCs differs in Zhang et al and Slavin et al.

Sachs may teach limitation (d). However, the combination of Sachs with the technique using TBI of Slavin et al and Ildstad et al would not lead a skilled artisan to the present

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invention, because none of these references disclose limitations (c) and (e) of the present invention.

In summary, Slavin et al, Ildstad et al, Zhang et al and Sachs do not disclose a technique suitable for a one-day protocol by which an engraftment rate of 100% can be achieved by employing the immunological tolerance technique using TBI. Thus, Applicants respectfully submit that a skilled artisan could not predict a technique achieving 100% engraftment according to a one-day protocol from any combination of Slavin et al, Ildstad et al, Zhang et al and Sachs.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Slavin et al alone or when combined with the teachings of Ildstad et al and Zhang et al, and Sachs and in any event, such a combination can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

SUGHRUE MION, PLLC

Telephone: (202) 293-7060

Facsimile: (202) 293-7860

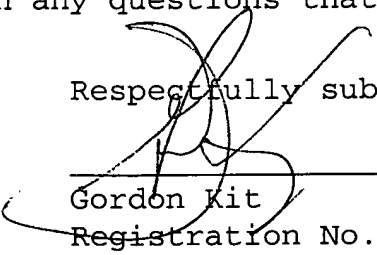
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Respectfully submitted,


Gordon Kit

Registration No. 30,764